

**REMARKS****I. Preliminary Remarks**

Claims 11-12 and 21-23 were objected to as being drawn to non-elected subject matter. In the foregoing amendment, claims 11-12 and 21-23 are canceled without prejudice. Applicant reserves the right to pursue claims to subject matter of the same or similar scope in a duly filed related application. Claims 24-26 and 35 are also objected to as multiple dependent claims that improperly depend from other multiply dependent claims. Claims 24-26 and 35 were amended appropriately in the foregoing amendment. These amendments do not include new matter.

**II. The Rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement should be withdrawn.**

The Examiner rejected claims 1-12, 17-18 and 21-23 under 35 U.S.C. § 112, first paragraph, stating that the specification does not reasonably provide enablement for any AAV vector other than AAV2 with insertions at the designated sites. The Examiner purportedly applied the factors set out in *In re Wands et al.*, 858 F.2d. 731, 737, 8 USPQ 2d 1400, 1404 (Fed. Circ. 1988) to evaluate whether carrying out the claimed invention requires undue experimentation. Applicants traverse this rejection.

In evaluating the nature of the invention, the Examiner stated that the specification provides for very specific sites for insertion of a target peptide in an AAV2 vector and does not teach the insertion sites in any other AAV serotypes. The Examiner asserts that identification of sites in other AAV serotypes would be unpredictable. Further, the Examiner stated that the manipulation of AAV vectors for altered tropism is a new and developing art. Submitted herewith is a Declaration of Jeffery Bartlett, Ph.D. under 37 C.F.R. § 1.132 (hereinafter "Declaration") that provides evidence that the identification of insertion sites in any AAV serotype is predictable in view of the teachings in the application and the state of the art.

The data presented in the declaration demonstrates that the three-dimensional structures of the AAV serotypes are predicted to be very similar. Importantly, the exposed regions are similarly located within the capsid protein. The exposed regions are preferred locations for the insertion sites in order to locate the target peptide on the surface of the

virion. While there is variability in the amino acid sequences among the AAV serotypes, the exposed regions of the capsid proteins are likely to be the locations of insertions that will not effect viral titer and infectability. Sequence alignments easily allow one of skill in the art to determine the location of insertion points of the invention and as demonstrated in the Declaration, computer modeling allows one of skill in the art to predict exposed regions within the three-dimensional structure of the capsid proteins. These means for predicting and confirming the three-dimensional structures of the capsid proteins of AAV serotypes were known in the art at the time of filing. Thus, the combination of the teaching in the specification and the techniques known in the art, allows one of skill in the art to carry out the invention in any AAV vector serotype without undue experimentation.

The Examiner points out that the working examples provided in the specification are carried out in the AAV2 vector and the regions of insertion within the capsid protein of the vector were determined by comparison to other parvovirus and not particularly AAV serotypes. As described in paragraphs 3 and 4 of the Declaration, the three-dimensional structure of five parvoviruses were known at the time of filing; however, no crystal structure of any AAV serotype was known. Computer models available in the art at the filing date were used to compare the known parvovirus three-dimensional structures with AAV serotypes to identify insertion sites. As demonstrated in Figure 2 of the Declaration, the computer predicted exposed regions of AAV2 are very similar to the regions discovered to be exposed once the crystal structure of AAV2 (Monkalenko *et al.*, *J. Virol.* 74(4):1761-1766, 2000) was solved after the filing date.

The Examiner used the difference in primary amino acid structure between AAV2, AAV3 and AAV4 as evidence that the art was unpredictable at the time of filing. However, as describe in paragraph 3 of the Declaration, the secondary structure of the capsid proteins is more relevant to identifying insertions sites within any capsid protein than the primary amino acid sequence. The effective insertion sites that do not affect viral titer and infectability are within the exposed regions of the capsid proteins. As displayed in Figures 3 and 4 (¶6) of the Declaration, the predicted three-dimensional structures of AAV1, AAV2, AAV3, AAV4 and AAV5 are very similar to the three-dimensional structure of AAV2.

The declaration also provides experimental data demonstrating that BAP epitope insertion at analogous sites in various AAV vectors (AAV1, AAV3, AAV4 and AAV5) did not prevent viral particle formation (See ¶10-12 and Fig. 7 of the Declaration). As described in paragraph 10 of the Declaration, the insertion sites in the various vectors were identified by aligning the amino acid sequences of the AAV serotypes and choosing regions that are predicted to be exposed to the surface. Therefore, the insertion sites were chosen based on the enabling teaching of the specification. The experiments demonstrate that the analogous insertions in various AAV vectors were as effective as those insertions in AAV2.

In view of the evidence provided in the Declaration and the foregoing remarks, Applicant requests that the rejection of claims 1-10 and 17-18 under 35 U.S.C. § 112, first paragraph, for lack of enablement be withdrawn.

**III. The rejection under 35 U.S.C. § 112, first paragraph, for lack of written description should be withdrawn.**

The Examiner rejected claims 1-12, 17-18 and 21-23 under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. In particular, the Examiner alleges that the specification does not provide the structural and functional characteristics used to identify the sites of insertion for vectors other than AAV2. Thus, the Examiner alleges that Applicant does not teach a representative number of species to adequately describe the genus of AAV vectors. Applicant traverses this rejection.

Five AAV serotypes were known in the art at the time of filing (AAV1: *J. Virol.* 72(1):309-319, 1998; AAV3: *Virology* 221(1):208-17, 1996; AAV4: *J. Virol.* 71(9):6823-33, 1997; AAV5: *J. Virol.* 73(2):1309-19, 1999). The Declaration demonstrates that the predicted secondary structures of the capsid proteins of these five AAV serotypes are very similar. In particular, the AAV serotypes are predicted to have similar regions exposed on the surface of the virus (see ¶7 and Figs. 3 and 4 of the Declaration). Thus, one of skill in the art would understand the specification describes the genus of AAV vectors recited in the claims.

The Examiner states that it is unclear what structural and functional characteristics should be used to identify the sites of insertion for AAV vectors. The specification states that the insertion sites of the present invention are at a position in the capsid protein that is exposed on the surface of an AAV vector and that location should not disrupt conformation of the capsid protein in a manner that prevents assembly of the vector or infectivity of the vector. (See page 5, lines 24-27). Thus, the structural characteristic to be used to identify the location of the insertion, as taught in the specification, is exposure to the surface. As demonstrated in the paragraph 6 of the Declaration, computer modeling based on the primary amino acid sequence allows one of skill in the art to identify regions of the capsid protein that are exposed to the virus surface. As stated in the specification, computer programs that predict secondary structure were readily available at the time of filing (see page 11, lines 21-27).

Therefore, applicant was in possession of the invention at the time of filing. Applicant requests that the rejection of claims 1-10 and 17-18 under 35 U.S.C. § 112, first paragraph, for lack of written description be withdrawn.

#### CONCLUSION

In view of the above, pending claims 1-10 and 17-18 are believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

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Respectfully submitted,

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